REMARKS

Claims 1-23 are pending in this application. Claim 4 has been canceled and claim 23 has been withdrawn, leaving claims 1-3 and 5-22 remaining. Claims have been canceled in the expectation that the amendments will place this application in condition for allowance.

The amendments do not introduce new matter within the meaning of 35 U.S.C. §132. Basis for the claim amendments is found in claims 1-23 as originally filed and elsewhere throughout the specification and claims. Accordingly, entry of the amendments is respectfully requested.

1. Objection to the Specification

The Office Action objects to the application because the specification fails to explicitly state a claim of benefit of priority to prior applications.

Applicant has amended the Specification to insert as paragraph one on page one of the specification an appropriate correction to state the benefit of priority to prior applications.

Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw the objection to the Specification.

2. Rejection of Claims 4 and 18 under 35 U.S.C. §112, second paragraph

The Office Action rejects claims 4 and under 35 U.S.C. §112, second paragraph, for the following reasons:

> Claims 4 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 is confusing in being dependent from Claim 1 because Claim 1 recites a method wherein the complex is formed in the presence of the modulator, while Claim 4 recites a method wherein the modulator is added after complex formation. Claim 18 is confusing in reciting a method wherein complex activity is monitored is detected separately from complex activity. It is suggested that the phrase "... and/or complex activity" at the end of Claim 18 be deleted.

Applicant has canceled claim 4 and amended claim 18 as suggested by the Examiner.

Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 4 and 18.

3. Rejection of Claims 1-22 under 35 U.S.C. §112, first paragraph

The Office Action rejects claims 1-22 under 35 U.S.C. §112, first paragraph, for the following reasons:

> [T]he specification is enabling for methods of screening for modulators of calcineurin activity in the presence of SOD as well as binding of calcineurin and SOD using the calcineurin and SOD variants of Examples 20-25. However, the specification is not enabling for methods of using any form of calcineurin or any form of SOD.

The Office Action further discusses, at some length, why the Examiner believes the Application to be deficient in showing how to modify calcineurin and/or SOD "for the selection of which of the infinite number of variants have the claimed property." The Office Action also discusses in some detail why the Examiner believes that "the specification fails to describe the structure of sufficient representative species of the large genera of all proteins having calcineurin or SOD activity such that a skilled artisan would recognize that applicants were in possession of the claimed invention."

Applicant respectfully traverses this rejection on the basis that, the discussion of "variants" and "a large genera of proteins" is only appropriate to an application which claims methods for ***using*** any form of calcineurin and/or any form of SOD. However, these arguments reflect a fundamental misunderstanding of the inventive subject matter, because the inventive subject matter is concerned with a method for ***screening*** for activity of only one Calcineurin/SOD combination at a time. A discussion about variants is irrelevant to the claimed invention.

Taking a proper understanding of the inventive subject matter in this application leads one to the inescapable conclusion that the minimal experimentation required to determine whether a particular Calcineurin/SOD combination has the desired

activity is nothing more than a routine experimental control which may, optionally, be completed before proceeding with the claimed methods for screening for modulators of that activity. Any chosen combination of calcineurin and SOD will either have an activity of interest or not. The experimentation required to run a positive control to determine whether there is such activity is not "undue experimentation." The claimed inventive subject matter assumes that one will screen for modulators of the desired activity only in those Calcineurin/SOD combinations which have an activity one wishes to modulate. Further, however routine determination of activity of a particular Calcineurin/SOD combination may be, this step is not required by the claimed subject matter, and one may screen for modulators of inactive Calcineurin/SOD combinations as well. In any event, the Examiner's argument that the Specification is "not enabling for ***methods*** of using any form of calcineurin or any form of SOD" (emphasis added) is misplaced in light of a correct reading of the claims.

Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 1-22 under 35 U.S.C. §112, first paragraph.

4. Rejection of Claims 1-5, 9, 13-16, 18, 19, and 21 under 35 U.S.C. §102(b)

The Office Action rejects claims 1-5, 9, 13-16, 18, 19, and 21 under 35 U.S.C. §102(b) as being anticipated by Wang, et al. As the basis for this rejection, the Office Action states:

> Claims 1-5, 9, 13-16, 18, 19, and 21, as written, do not limited the scope of the invention to methods for screening of modulators of calcineurin enzymatic activity wherein said methods are characterized in that a direct interaction between calcineurin and SOD is monitored.

Applicant respectfully traverses this rejection on the basis that the '989 patent fails to teach the claimed subject matter. Applicant's claims as presently amended are directed to a method for screening for a modulator of calcineurin enzymatic activity, characterized in that a direct interaction between calcineurin and superoxide dismutase is monitored.

By contrast, Wang, et al. disclose only that calcineurin and SOD co-elute, in part, on gel filtration. The word "complex" or the concept of a direct relationship is not disclosed in Wang, et al. to describe the calcineurin/SOD relationship.

To constitute anticipation under 35 U.S.C. §102, all material elements of a claim must be formed in one prior art source. In re Marshall, 577 F.2d 301, 198 USPQ 344 (CCPA 1978); In re Kalm, 378 F.2d 959, 154 USPQ 10 (CCPA 1967). As the Examiner admits, Wang, et al. does not disclose the direct

complex formation and activity as claimed herein. Thus, in the absence of any teaching in Wang, et al. that the direct interaction between calcineurin and SOD produces enzymatic activity and that this activity can be modulated, Wang, et al. does not anticipate the present claims.

Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw this rejection.

5. Rejection of Claims 5-12, 15, and 17 under 35 U.S.C. §103(a)

The Office Action rejects claims 5-12, 15, and 17 under 35 U.S.C. §103(a) as being unpatentable over Wang, et al., in view of one of Brown, et al., 1997; claim 9 as being unpatentable over Wang, et al., in view of Woodrow, et al., 1993; claims 10-12 as being unpatentable over Wang, et al., in view of Lau, et al., 1996 or Robbins, et al., 1993, and further in view of Aramburu, et al, 1998; and claims 5, 15, and 17 as being unpatentable over Wang, et al., in view of admission of availability, Specification page 28, lines 21-24. As the basis for this rejection, the Office Action refers to the reasons stated in the prior Office Action and states:

> Regarding applicant's argument II, neither Claim 19 or claims dependent thereon are rejected under 35 U.S.C. 103(a). Regarding Claim 1 and claims dependent thereon, as described above in the response to the applicant's arguments in response to the anticipation rejection, Wang et al do show that calcineurin forms a complex with SOD.

Regarding applicant's argument III, as stated in-the prior action Wang et al do show that calcineurin forms a complex with SOD. Thus in the prior action, the secondary references of Brown et al, Woodrow et al, Lau et al, Robbins et al, and Aramburu et al were not used to establish that calcineurin forms a complex with SOD but to remedy the deficiencies of Wang et al. Regarding the secondary references applicants admit the following. That Brown et al, does teach the use of fluorescence-labeled proteins for assaying protein-protein interaction, that Woodrow et al does teach regulation of calcineurin in cells, that Lau et al teach the use of his-tagged fusion proteins, that Robbins et al teach the purification of his-tagged proteins (Examiner's note: they use NTA-metal affinity chromatography), and that Aramburu et al address binding of calcineurin. Thus, these references provide evidence that it would be obvious to a person of ordinary skill in the art to modify the methods of Wang et al to: use calcineurin and/or SOD labeled with green fluorescent protein (Claim 6), express calcineurin and/or SOD as fluorescent proteins (Claim 7), monitor complex formation using laser fluctuation correlation spectroscopy (Claim 8), use the method of Claim 1 wherein complex formation is performed within the cell (Claim 9), to isolated calcineurin and/or SOD prior to complex formation (Claim 10), use the method of Claim 10 wherein purification of calcineurin or SOD is achieved by NTA metal affinity chromatography (Claims 11 and 12), and use a peptide substrate labeled with fluorescein (Claim 17).

Regarding applicant's argument I regarding motivation and expectation of success in using the methods of Brown et al, Woodrow et al, Lau et al, Robbins et al, and/or Aramburu et al to remedy the deficiencies of Wang et al, one would be motivated by the desire to determine whether modulators of calcineurin affect binding between calcineurin and SOD. The expectation of success is high, as all of the techniques used to demonstrate protein-protein interaction, which are deficiencies of Wang et al, were standard in the art, as shown by Brown et al, Woodrow et al, Lau et al, Robbins et al, or Aramburu et al.

Applicant respectfully traverses this rejection. To establish a *prima facie* case, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Second the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art reference must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

As noted earlier, the Examiner concludes, without reference to a page and line number, that Wang, et al. "show that calcineurin forms a complex with SOD." Contrary to the Office Action, Wang, et al. shows only that calcineurin co-elutes with SOD. In fact, Wang et al. teaches that the small inactivator acts by inhibiting superoxide dismutase rather than by acting directly on Calcineurin (page 436, lines 12 to 14). That means that the small inactivators just influence the activity of superoxide dismutase. As outlined on page 436, lines 20 to 22,

the superoxide dismutase probably protects Calcineurin by preventing oxidation of the catalytic center of Calcineurin. This is an enzymatical process caused by superoxide dismutase. Such an enzymatical interaction has nothing to do with a complex formation. Consequently, there is no disclosure of complex formation in Wang, et al.

As presently amended, the inventive method is directed only to the monitoring of complex formation and not to enzymatic activity. Preferred embodiments of the monitoring of complex formation are outlined, for example, in dependent claims 5 to 8. Consequently, the method according to the present claims is novel over Wang, et al., without doubt. In the state of the art, and especially in Wang, et al., nothing is said about complex formation between Calcineurin and SOD, and especially nothing is said about a direct interaction between Calcineurin and superoxide dismutase. In Wang et al. there is no hint to study the complex formation between Calcineurin and superoxide dismutase, especially not in order to screen for a modulator of Calcineurin enzymatic activity. There is no motivation to use any methods of the state of the art concerning investigation of protein-protein interactions, because nothing is said about direct protein-protein interaction between Calcineurin and superoxide dismutase in the primary reference, Wang, et al.

Consequently the method according to the present claims is not only novel but also unobvious over the prior art of record.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be enabled, novel, and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of remaining claims 1-3 and 5-22, and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

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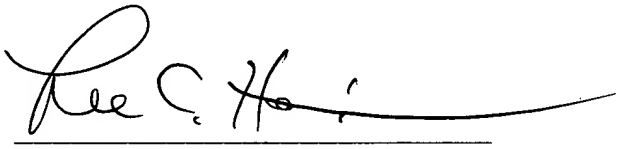
Date: December 1, 2003 By: 

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